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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,950	07/07/2000	George R. Pettit	5368-US	4557

7590 09/29/2004

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EXAMINER
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ZUCKER, PAUL A

ART UNIT	PAPER NUMBER
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1621

DATE MAILED: 09/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/582,950	<b>Applicant(s)</b> PETTIT ET AL.	
	<b>Examiner</b> Paul A. Zucker	<b>Art Unit</b> 1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 12 July 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 11-41 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 11-22,30,40 and 41 is/are allowed.
- 6) ☒ Claim(s) 23-29 and 31-38 is/are rejected.
- 7) ☐ Claim(s) 39 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 July 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Upon consideration of Applicant's Request for Reconsideration of the restriction requirement, the Examiner hereby withdraws the previous restriction requirement. Claims 11-41 are the subject of the following Office Action and have been examined fully on the merits.

### ***Specification***

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.
3. This application does not contain a section headed "Brief Description of the Drawings". Appropriate correction is required.
4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 recites the limitation "wherein the phosphine is

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selected from" in line 1 and further recites in line 4 "dibenzyl N, N-diethylphosphoramidate" which is not a phosphine. The intended scope of claim 25 is therefore unclear and claim 25 is rendered indefinite.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 23, 24 and 26-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Rathbone et al (WO92/16486-A1 10-1992). NOTE: For the purposes of this rejection N,N-diethylphosphoramidate is considered a phosphine (Cf. claim 25). Rathbone discloses (Page 11, line 16-page 14, line 19) a process for the synthesis of Combretastatin A4 Phosphate potassium salt. Rathbone's process employs N, N-diethylphosphoramidate at  $-70^{\circ}\text{C}$  in THF followed by addition of MCPBA in dichloromethane to produce the ammonium salt which is then converted to the dipotassium salt. Rathbone therefore anticipates claims 23, 24 and 26-29.
7. Claims 33-35 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Petit (US 5,561,122 10-1996). Petit discloses (Column 3, line 46- column 4, line 12) the compounds disodium and dipotassium combretastatin A-4 3-O-phosphate. Petit further discloses (Column 4, line 14- column 5, line 16) the use of pharmaceutical

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formulations for the modulation of tumor growth. Petit therefore anticipates claims 33-35 and 37.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35

U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 31-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petit (US 5,561,122 10-1996) in view of Hochlowski et al (US 5,484,799 01-1996).

Instantly claimed are alkali and alkaline earth metal salts of combretastatin A-4 3-O-phosphate excluding sodium and potassium.

Petit teaches (Column 3, line 46- column 4, line 12) forming the compounds disodium and dipotassium combretastatin A-4 3-O-phosphate from the corresponding ammonium hydrogen salt. The direct formation from the diacid, eliminating the unnecessary formation of the ammonium salt, would have been

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obvious to one of ordinary skill in the art. Petit further teaches (Column 4, line 14-column 5, line 16) the use of pharmaceutical formulations for the modulation of tumor growth.

The difference between the compounds taught by Petit and those instantly claimed is that alkali metal salts other than sodium and potassium are claimed and Petit does not suggest other alkali metal salts.

Hochlowski, however, teaches (Column 2, lines 36-51) the equivalence, for pharmaceutical purposes, of the lithium, potassium, sodium, calcium, magnesium and ammonium salts.

One of ordinary skill in the art would have been motivated by Hochlowski to substitute the sodium and potassium salts with the corresponding lithium, calcium and magnesium salts since they would be expected to have the same pharmaceutical properties. There would have been a reasonable expectation for success based upon Hochlowski's teaching of the equivalence of the various cations.

Thus the instantly claimed compounds and methods for their use would have been obvious to one of ordinary skill in the art.

***Claim Objections***

9. Claim 39 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Allowable Subject Matter***

10. Claim 39 is drawn to allowable subject matter. Claims 11-22, 30, 41 and 42 are allowed. The following is a statement of reasons for the indication of allowable subject matter: Atherton et al (Journal of the Chemical Society, 1947, pages 674-678) teaches (Paragraph bridging pages 675 and 676) the instantly employed method for phosphorylation. Atherton suggests (Abstract) that the method can be used to phosphorylate ethyl alcohol but does not teach or fairly suggest that it can be used to phosphorylate phenolic hydroxyl groups. The instantly claimed process is therefore patentable over the teachings of Atherton.

The instantly claimed method of use of salts of combretastatin A-4 3-O-phosphate for the modulation of microbial growth is neither taught nor fairly suggested by Pettit and is therefore patentable over Pettit's teachings.

***Conclusion***

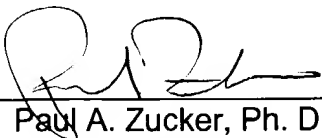
11. Claims 11-41 are pending. Claims 23-29, 31-38 are rejected. Claim 39 is objected to. Claims 11-22, 30, 40 And 41 are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 571-272-0650. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Patent Examiner  
Technology Center 1600